IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: FOSAMAX (ALENDRONATE SODIUM) PRODUCTS LIABILITY LITIGATION THIS DOCUMENT RELATES TO: ALL ACTIONS	MDL No. 2243 Master Docket No. 3:08-cv-08 DOCUMENT FILED ELECTRONICALLY

DEFENDANT MERCK SHARP & DOHME CORP.'S BRIEF IN SUPPORT OF PREEMPTION IN LIGHT OF THE SUPREME COURT'S DECISION IN *MERCK, SHARP & DOHME CORP. V. ALBRECHT*, 139 S. CT. 1668 (2019)

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INTRODUCTION

Six years ago, after a full trial and extensive briefing by the parties, Judge Pisano concluded that federal law preempted Plaintiffs' state law failure-to-warn claims against Merck Sharp & Dohme Corporation. Merck had shared with the FDA all the data about the possible link between its medicine Fosamax and certain "atypical" bone fractures, this Court determined, and had even proposed adding a warning about those fractures to the drug label. Yet the FDA rejected that proposal, because it did not believe—based on the then-available data—that there was enough evidence of a causal link. Based on those findings, this Court held that federal law prohibited Merck from adding a warning about these atypical fractures.

After a long trip up and then down the appellate ladder, these cases are now back in this Court—but everything Judge Pisano held before remains correct. Initially, the Third Circuit vacated this Court's decision on the ground that preemption presented a question for the jury (not the judge) and triggered a heightened standard of proof (clear-and-convincing evidence). But the Supreme Court disagreed in both respects, holding that judges must adjudicate preemption using ordinary standards of proof. That is exactly what Judge Pisano did. Nothing in the appellate proceedings or decisions calls for revisiting his analysis or conclusions.

Judge Pisano was right. As the Supreme Court reiterated, preemption applies when a fully informed FDA declines to approve the warning at issue. Here, Plaintiffs have long abandoned any claim that Merck failed to keep the FDA fully informed. And the FDA advised Merck in official correspondence that the agency would not approve its proposed warning about atypical fractures. Plaintiffs' theory is that the FDA rejected the warning based on *semantic* objections, not *scientific* ones, but that account is refuted by the regulatory context, the agency's contemporaneous statements and actions, and the agency's later statements and actions; indeed, it is refuted by the agency's representations to the Supreme Court *in this case*. Judge Pisano correctly rejected it.

REGULATORY AND FACTUAL BACKGROUND

A. The FDA's Gatekeeping Role in Prescription Drug Labeling.

Congress has charged the FDA with ensuring that every prescription drug on the market is "safe for use under the conditions prescribed, recommended, or suggested" in its "labeling." 21 U.S.C. § 355(d). As that command suggests, labeling is the "centerpiece" of the FDA's risk management strategy for approved drugs, and the primary means by which the FDA communicates its conclusions about drug safety. FDA, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3944 (Jan. 24, 2006).

The FDA thus has final say over a prescription drug's label throughout the drug's lifespan. At the outset, before a new drug may be distributed, the manufacturer must submit for FDA approval "the labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1). And, after physicians begin prescribing a drug, the manufacturer must obtain the FDA's approval for labeling changes that become warranted as a result of new safety information. The manufacturer may seek that approval either *concurrently* with its revisions to the label (through the "Changes Being Effected" or "CBE" process) or *before* making the revisions (through the "Prior Approval Supplement" or "PAS" process). When "significant questions exist on whether to revise or how to modify existing drug labeling," the FDA has historically "accepted PAS applications instead of CBE supplements." Br. of the United States as *Amicus Curiae* in Support of Certiorari, *Merck, Sharp & Dohme Corp. v. Albrecht*, No. 17-290, at *5 (May 22, 2018) ("U.S. Cert. Br.") (attached as Exhibit 11). Using the PAS process avoids the risk that the FDA rejects the revision and orders the manufacturer to "cease distribution" of the drugs that already bear the rejected label, 21 C.F.R. § 314.70(c)(7), which would cause confusion throughout the medical community. For this reason, "manufacturers typically consult with FDA *prior to* adding risk information to labeling." 71 Fed. Reg. at 3934 (emphasis added).

Whichever process the manufacturer invokes, the agency's ultimate review is the same: The labeling change will be approved only if "the evidence of a causal association satisfies the standard for inclusion in the labeling" under the FDA's regulatory standards. 21 C.F.R. § 314.70(c)(6)(iii)(A); *see also id.* § 314.125(b)(6), (b)(8). The standard for inclusion depends on which section of the label is involved. To merit inclusion in the "Warnings and Precautions" section, the risk must be "clinically significant" and there must be "reasonable evidence of a causal association" between the drug and the reaction. *Id.* § 201.57(c)(6)(i). By contrast, any "undesirable effect" may be listed on the "Adverse Reactions" section of the label, so long as there is "some basis to believe" that a "causal relationship" exists. *Id.* § 201.57(c)(7).

The FDA also has its own, independent statutory obligation to ensure that drug labels reflect the latest medical science. If the agency "becomes aware of new information, including any new safety information," that "should be included in the labeling of the drug," the FDA "shall promptly notify the [manufacturer]." 21 U.S.C. § 355(*o*)(4)(A). After the manufacturer shares its position on the new information, the FDA must "initiate discussions" to resolve any disagreement about next steps. *Id.* § 355(*o*)(4)(B), (*o*)(4)(C). In the end, of course, the FDA has the final say; it "may issue an order directing ... such a labeling change as the [agency] deems appropriate to address the new safety or new effectiveness information." *Id.* § 355(*o*)(4)(E).

The FDA has other powers and duties related to pharmaceutical safety too. Congress has, for instance, instructed the FDA to communicate with the public about drug safety through a website that links to its "most recent safety information and alerts," like "product recalls, warning letters, and import alerts." *Id.* § 355(r)(1), (r)(2)(B)(iv).

B. Merck Tries To Update Fosamax's Label.

These cases concern the labeling for Merck's medicine alendronate sodium, known as Fosamax, which the FDA approved to prevent and treat osteoporosis in postmenopausal women.

In healthy bone tissue, old bone cells are replaced by new ones in unison. *See, e.g.*, Liza J. Raggatt & Nicola C. Partridge, *Cellular and Molecular Mechanisms of Bone Remodeling*, 285 J. Biological Chem. 25103, 25103–07 (2010). In post-menopausal women, however, "the rate of bone resorption" (the process that breaks down old bone cells) "exceeds that of bone formation, thereby causing bone loss" and threatening to increase the risk of "osteoporotic fracture." *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 852 F.3d 268, 272 (3d Cir. 2017), *vacated on other grounds sub nom. Merck, Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668 (2019). Fosamax and other bisphosphonates "slow the resorption process, restoring the balance between resorption and formation and reducing the risk of osteoporotic fracture." *Id.* The drug has been reported to reduce the risk of "vertebral fracture (by 40% to 70%), hip fractures (by 20% to 50%), and nonvertebral fractures (by 15% to 39%)." Robert A. Adler, et al., *Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research*, 31 J. Bone & Mineral Research 16, 16–17 (2015).

Some scientists have theorized that antiresorptive drugs like Fosamax could potentially lead to oversuppression of bone turnover, which in turn could increase the risk of certain fractures. *See Fosamax*, 852 F.3d at 272, 274. Ordinarily, the resorption process removes "microcracks" that develop in otherwise-healthy bone tissue. *See id.* at 272. By slowing the resorption process, some have speculated that bisphosphonates may allow microcracks to accumulate, leading to "incomplete bone fractures called 'stress fractures.'" *Id.* The term "stress fracture" often "connotes a fracture resulting from excessive loading of a normal bone," but an "insufficiency stress fracture" is "caused by normal loading of poor-quality bone." *Id.*; *see also, e.g.*, *Dorland's Illustrated Medical Dictionary* 710–11 (29th ed. 2000) (defining an "insufficiency f[racture]" as "a stress fracture that occurs during normal stress on a bone of abnormally decreased density").

Left untreated, insufficiency stress fractures "may … develop [into] what are [now] known as 'atypical femoral fractures': severe, non-traumatic, low-energy complete fractures of the femur." *Fosamax*, 852 F.3d at 272.

Before Fosamax's original approval in 1995, "Merck scientists and third-party researchers discussed the possibility that antiresorptive drugs could inhibit a bone's ability to repair microdamage, potentially leading to stress fractures." *Id.* at 275. But when the FDA approved Fosamax, "it did not require Merck to include a warning about bone fractures." *Id.*

Leading up to 2008, a number of reports and case studies raised "the possibility" that Fosamax use was associated with femoral fractures. *Id.* At all times, "Merck kept the FDA informed of these and other studies suggesting a possible association between bisphosphonates and fractures." *Id.* "In March 2008," for example, "Merck submitted a periodic safety update to the FDA that included over 30 pages of information regarding atypical femoral fractures and suppression of bone turnover." *Id.* Later that month, "Merck forwarded to the FDA a letter published in the *New England Journal of Medicine* describing a 'potential link between [bisphosphonate] use and low-energy fractures of the femur.'" *Id.* (alteration in original). In June 2008, the FDA informed Merck (and other bisphosphonate manufacturers) that it was "aware of reports regarding the occurrence of subtrochanteric hip fractures in patients using bisphosphonates"[1] and asked the manufacturers to submit any "investigations" or "reports" they had about these unnamed "femoral fractures." *Id.* Of course, "Merck promptly complied." *Id.*

Although Merck did not, at that time, believe that the evidence established that "treatment with alendronate increases the risk of low-energy subtrochanteric and/or proximal femoral shaft

[1] The "subtrochanteric" part of the femur can be found, as its name suggests, below the "trochanters," which are the bony protuberances that join the femur to the hip. The "diaphyseal" region of the femur is the long shaft.

fractures," Merck reasoned that it was still "important to include an appropriate statement about them in the product label" given their "clinical importance" and "temporal association with bisphosphonate use." Exhibit 1 at A2697.[2] Accordingly, in September 2008, "while the FDA was analyzing Merck's data, Merck submitted a PAS to the FDA" seeking to revise Fosamax's label to account for this possible risk. *Fosamax,* 852 F.3d at 276.[3]

Specifically, Merck sought to revise the label in two ways. *First*, Merck sought to add "low-energy femoral shaft fracture" to the list of Adverse Reactions. Exhibit 1 at A2732. *Second*, Merck sought to add the following to the Warnings & Precautions[4] section of the label:

> Low-Energy Femoral Shaft Fracture
>
> Low-energy fractures of the subtrochanteric and proximal femoral shaft have been reported in a small number of bisphosphonate-treated patients. Some were stress fractures (also known as insufficiency fractures) occurring in the absence of trauma. Some patients experienced prodromal pain in the affected area, often associated with imaging features of stress fracture, weeks to months before a complete fracture occurred. The number of reports of this condition is very low, and stress fractures with similar clinical features also have occurred in patients not treated with bisphosphonates. Patients with suspected stress fractures should be evaluated, including evaluation for known causes and risk factors (e.g., vitamin D deficiency, malabsorption, glucocorticoid use, previous stress fracture, lower extremity arthritis or fracture, extreme or increased exercise, diabetes mellitus, chronic alcohol abuse), and receive appropriate orthopedic care. Interruption of bisphosphonate therapy in patients with stress fractures should be considered, pending evaluation of the patient, based on individual benefit/risk assessment.

Fosamax, 852 F.3d at 276.

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[2] For the Court's convenience, Merck generally refers to the page numbers from the Third Circuit Appendix ("A___"), located on the bottom-right corner of each exhibit page. The cover page to each exhibit identifies the original record source of the material in that exhibit.

[3] Technically, Merck submitted three such supplements, one for each approved formulation of Fosamax. These three were indistinguishable in all respects relevant here.

[4] In 2006, the FDA combined what used to be separate "Warnings" and "Precautions" sections into a single section. *See* 71 Fed. Reg. at 3946. The FDA did not require all manufacturers to immediately convert their existing labels into the new format, and so sometimes the underlying documents here refer only to the "Precautions" section.

To support its request, Merck provided a host of materials addressing the possible link between bisphosphonate use and these unusual fractures. *See, e.g.*, *id.* (noting that Merck "cited to nine articles reporting cases of low-energy femoral fractures"); Exhibit 1 at A2752 (reports of "low-energy subtrochanteric / mid femoral shaft fractures"); *see also* Exhibit 1 at A2757, A2751. Merck's supporting materials also explained its terminology: It used "stress fracture" in connection with reports of "low-energy subtrochanteric/mid femoral shaft fractures" to refer to "insufficiency fracture[s]" that occurred with no "identifiable external trauma." Exhibit 1 at A2751–52.

C. The FDA Rejects Merck's Request.

As a general matter, the FDA "communicate[s] with applicants about scientific, medical, and procedural issues that arise" in its review of requests for regulatory action. 21 C.F.R. § 314.102(a). If the agency spots "easily correctable deficiencies," it will "make every reasonable effort to communicate" those deficiencies "promptly," so as "to permit applicants to correct" them "relatively early in the review process." *Id.* § 314.102(b). And "if the only deficiencies ... concern editorial or similar minor deficiencies in the draft labeling," the "FDA will approve" the application "conditioned upon the applicant incorporat[ing] the specified labeling changes exactly as directed." *Id.* § 314.105(b); *see also* Br. of the United States as *Amicus Curiae* in Support of Petitioner, *Merck Sharp & Dohme Corp. v. Albrecht*, No. 17-290, at *5–6 (September 20, 2018) ("U.S. Merits Br.") (attached as Exhibit 12) (explaining the FDA's procedures).

The FDA applies similar protocols in the context of complete response letters ("CRLs"), the kind of response that Merck received to its PAS on May 22, 2009. Exhibit 2 at A1500–02. The FDA "will send the applicant" such a letter "if the agency determines that [it] will not approve the application … in its present form." 21 C.F.R. § 314.110(a). "A complete response letter will describe all of the specific deficiencies that the agency has identified." *Id.* § 314.110(a)(1). "When possible," a CRL "will recommend actions that the applicant might take to place the application

… in condition for approval." *Id.* § 314.110(a)(4). After receiving a CRL, the applicant must either "[r]esubmit the application" after "addressing all deficiencies identified," "[w]ithdraw the application," or "[a]sk the agency to provide … for a hearing" on its decision. *Id.* § 314.110(b); *see also* U.S. Merits Br., Exhibit 12 at *31–32 (explaining the FDA's CRL procedures).

In its CRL, the FDA accepted one of Merck's proposed additions (subject to rewording it), but rejected the other. As to the Adverse Reactions section (which, as noted above, requires only "some basis to believe" that there is a causal link between the drug and the adverse effect), the FDA approved the addition of "low energy femoral shaft *and subtrochanteric* fractures"—with the italicized words added by the FDA to Merck's proposed language. Exhibit 2 at A1501; *compare* Exhibit 1 at A2732. But, as to the Warnings & Precautions section (which, as noted, implicates the higher standard of "reasonable evidence of a causal association"), the FDA flatly *rejected* Merck's requested revision for the following three, independent "reasons":

> [Y]our justification for the proposed PRECAUTIONS section language is inadequate. Identification of "stress fractures" may not be clearly related to the atypical subtrochanteric fractures that have been reported in the literature. Discussion of the risk factors for stress fractures is not warranted and is not adequately supported by the available literature and postmarketing adverse event reporting.

Exhibit 2 at A1500–01.

The FDA's split decision tracked Merck's back-and-forth with agency officials during the agency's review. In April 2009, an FDA liaison told Merck by email that the FDA "would only approve a reference to atypical fractures in the 'Adverse Reactions' section." *Fosamax*, 852 F.3d at 277. "If Merck agree[d] to hold off on the W[arnings] & P[recautions] language at this time," the official suggested, "then [the FDA] c[ould] go ahead and close out these supplements." Exhibit 3 at A1498. It "would then work with [the Office of Surveillance and Epidemiology] and Merck to decide on language for a W&P atypical fracture language, if it [wa]s warranted." *Id.*

Around the same time, Merck representatives had a call with Dr. Scott Monroe—the FDA official who would soon draft the CRL. According to Merck's "internal notes," Dr. Monroe stated that "the FDA could agree to add language in the Adverse Reactions section of the label." *Fosamax*, 852 F.3d at 276–77. But Dr. Monroe also told Merck that its "elevation of this issue to a precaution" was "prolonging review" because, among other reasons, "the conflicting nature of the literature d[id] not provide a clear path forward." *Id.* at 277.

In June 2009, after receiving the CRL, Merck did as the FDA instructed. It "withdr[ew] the prior approval supplement" that it had submitted. Exhibit 4 at A2963. Then it submitted a "Changes Being Effected Submission" that included the FDA-edited revisions to the Adverse Reactions section of the label, but no change to the Warnings & Precautions section. *Id.*

D. After Publication of a New Report, the FDA Orders a Revised Warning.

The FDA continued to review the possible relationship between long-term bisphosphonate use and atypical femoral fractures, but did not change its position about the need for a warning until the publication of a transformative report in September 2010.

Before that time, the FDA consistently maintained that the evidence did not support a link between Fosamax and atypical fractures. In March 2010, it issued a Drug Safety Communication on the topic. *Fosamax*, 852 F.3d at 278. The FDA noted that its review of manufacturer-submitted data "did not show an increase in th[e] risk" of "atypical subtrochanteric femur fractures" "in women taking these medications." Exhibit 5 at A1508; *see also id.* (noting a separate December 2008 study that showed "similar numbers of atypical subtrochanteric femur fractures relative to classical osteoporotic hip fractures" in patients who used and did not use bisphosphonates); *id.* (noting that "the data … reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures"). Accordingly, the FDA instructed doctors to "continue to follow the recommendations in the drug label." *Id.*

The agency also noted, however, that it was "working closely with outside experts," including a task force assembled by the American Society for Bone and Mineral Research, "to gather additional information that may provide more insight into this issue." *Id*. The next day, the American Society of Bone and Mineral Research echoed these points in its own public statement. While "[r]ecent reports suggesting a link between long-term bisphosphonate usage and rare bone fractures" called for further study, "[h]ealthcare professionals" were advised to "[c]ontinue following drug label recommendations when prescribing oral bisphosphonates." Am. Soc'y for Bone & Mineral Research, ASBMR Task Force Reviewing Link Between Fractures and Bisphosphonate Therapy (Mar. 11, 2010), *available at* https://tinyurl.com/qn8qzy8.

In September 2010, the task force made public its first report. It crafted a "provisional case definition" of the "features for complete and incomplete atypical [femoral] fractures" and then reassessed prior studies in light of that definition. Elizabeth Shane, et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research*, 25 J. Bone & Mineral Research 2267, 2268–69 (2010) ("*First Report*"). Although "a causal association between [bisphosphonates] and atypical fractures ha[d] not been established," the task force's analysis "suggest[ed] that the risk rises with increasing duration of exposure," and so the task force recommended that "[p]hysicians and patients should be made aware of the possibility of atypical femoral fractures." *Id.* at 2267.[5]

[5] With respect to terminology, the report observed that "[t]he radiologic presentation of atypical femoral fractures bears striking similarities to that of stress fractures." *First Report* at 2270. Indeed, the task force's second report, a few years later, would confirm what Merck had long suspected: that atypical femoral fractures "*are* [ordinary] stress fractures" that, left untreated, may progress into complete "insufficiency fractures." Elizabeth Shane, et al., *Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research*, 29 J. Bone & Mineral Research 1, 10–12 (2014) ("*Second Report*") (emphasis added).

The FDA responded immediately. First, in September 2010, it issued another "Drug Safety Communication," noting that the report's findings would "facilitate future studies" assessing any causal link between "these unusual femur fractures" and bisphosphonate use. *Fosamax*, 852 F.3d at 278; Exhibit 9 at A1512. "Regarding the task force's recommendation of a label change, the FDA stated that it 'ha[d] assembled and [wa]s thoroughly reviewing all long term data available on the products, as well as all safety reports' and would be 'considering label revisions.'" *Fosamax*, 852 F.3d at 278. Then, the next month, the FDA announced that it would require all bisphosphonate manufacturers to add warnings about atypical fractures because "'these unusual femur fractures have been predominantly reported in patients taking bisphosphonates.'" *Id.* The FDA's Deputy Director of the Office of New Drugs expressly identified "the task force report" as having "made the FDA 'confident' that atypical femur fractures are 'potentially more closely related to' long-term use of bisphosphonates 'than [the FDA] previously had evidence for.'" *Id.* (quoting Exhibit 6 at A1392–93) (alterations in *Fosamax*)).

Citing both the new task force report and the agency's duties under 21 U.S.C. § 355(*o*), the FDA wrote to Merck (and the other relevant manufacturers) to propose changes to the Warnings & Precautions section of their drugs' labels. Exhibit 7 at A1515–19. "Merck responded by proposing additional language that, according to Merck, was intended to make clear that doctors should attempt to rule out [ordinary] stress fractures." *Fosamax*, 852 F.3d at 279. The FDA rejected Merck's efforts; in its view, "for most practitioners, the term 'stress fracture' represents a minor fracture and this would contradict the seriousness of the atypical femoral fractures associated with bisphosphonate use." *Id.* (quoting Exhibit 8 at A1540). "The FDA subsequently approved language nearly identical" to its original proposal, and that language remains on Fosamax's label to this day. *Id.*

E. The District Court Rejects Plaintiffs' Failure-To-Warn Claims.

More than a thousand individuals sued Merck, alleging that they suffered femoral fractures because they took Fosamax. The actions were consolidated into this MDL. Plaintiffs' complaints included causes of action that, in one way or another, turned on Merck's alleged failure to warn them, on Fosamax's label, of the risk of atypical fractures. *See id.* at 279–80.

With the parties' help, Judge Pisano selected several bellwether cases for trial. *See In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, MDL No. 2243, 2014 WL 1266994, at *1–2 (D.N.J. Mar. 26, 2014) ("*OTSC Opinion*"), *vacated and remanded*, 852 F.3d at 302. After discovery in one of those cases, known as *Glynn*, Merck moved for summary judgment on the ground that the failure-to-warn claims were preempted by federal law.

Under the Supreme Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009), such claims are preempted if the FDA "would have prevented [the manufacturer] from adding a stronger warning" to the drug's label. *Id.* at 573. Here, of course, the FDA did, in fact, prevent Merck from revising its label before the issuance of the ASBMR task force report. The district court "reserved judgment" on Merck's motion (as well as analogous motions made during trial) to allow the parties to "develop[] a full record." *Fosamax*, 852 F.3d at 280. Post-trial, the court allowed Plaintiffs to "present more evidence," and then held that Glynn's failure-to-warn claims were preempted. *See In re Fosamax (Alendronate Sodium) Prods. Liab. Litig.*, 951 F. Supp. 2d 695, 697, 701 (D.N.J. 2013) ("*Glynn Opinion*"), *vacated and remanded*, 852 F.3d at 302.

Although he acknowledged that impossibility preemption is a "demanding defense," Judge Pisano held that Merck met that high bar because "clear evidence exist[ed] that the FDA would not have approved a label change to the Precautions section … prior to Mrs. Glynn's fracture" in April 2009. *Id.* at 703. Merck had "provide[d] all the information it had on femur fractures to the FDA." *Id.* at 705. Yet the agency rejected Merck's PAS seeking to warn about that risk, and that

decision—illuminated by the regulatory context and by the back-and-forth between Merck and the FDA—"indicat[ed] that [the FDA] would not accept a label change … at that time." *Id.* at 703. Although Plaintiffs contended that the FDA had "rejected [Merck's PAS] due to language, specifically the use of 'stress fracture' instead of" the term "atypical femoral fracture," the district court rejected that account. *Id.* at 704. Plaintiffs' own expert used stress-fracture language in connection with atypical femoral fractures, and Merck's regulatory expert testified, after reviewing the regulatory record, that the FDA rejected Merck's proposal because the "data didn't support the precaution language," not because it was "confusing to doctors" or because "stress fractures didn't look as severe and significant." *Id.* (alterations in original). This Court agreed.

After the district court's decision in *Glynn*, the court ordered other Plaintiffs whose injuries occurred before publication of the task force's report to show cause why their claims were not also preempted. *OTSC Opinion*, 2014 WL 1266944, at *6. After giving those Plaintiffs "yet another opportunity to brief the issue," the court ruled against them as well. *Id.* at *8. Plaintiffs' contention that Merck "withheld information from the FDA" was "based largely on speculation" and thus "c[ould not] defeat summary judgment." *Id.* at *17. And despite Plaintiffs' "new" expert opinion about the import of the evidence in *Glynn*, there remained "clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning." *Id.* at *16. Therefore, these Plaintiffs' failure-to-warn claims—along with their "disguised" failure-to-warn claims, such as their nominal "design defect" claims that really hinged on the failure to warn—were also preempted. *See id.* at *13, 16–17.[6]

[6] The district court also granted Merck summary judgment on claims based on Merck's alleged failure to update the Adverse Reactions section of the Fosamax label before June 2009. *See OTSC Opinion*, 2014 WL 1266944, at *14–16. The Third Circuit vacated and remanded the order on those claims, *see Fosamax*, 852 F.3d at 300–02, and Merck did not seek review of that decision before the Supreme Court. Those distinct claims are not at issue at this time.

F. The Third Circuit Vacates and Remands for a Jury To Decide Preemption Under a Heightened Standard.

On appeal, the Third Circuit vacated and remanded the district court's preemption decision. The Court of Appeals did not dispute the trial court's finding that "Merck kept the FDA informed" about the developing science regarding "a possible association between bisphosphonates and fractures." *Fosamax*, 852 F.3d at 275. Nor did it disagree, *per se*, with the court's determination that the FDA would have rejected any warning about atypical femoral fractures before the task force issued its report. *See, e.g.*, *id.* at 297 (refusing to "discount the force" of Merck's evidence on this point). Rather, the Third Circuit concluded that preemption presented "a question of fact for the jury," not a question of law for the judge. *Id.* at 293. And, in answering that question, the Third Circuit held that the jury must apply a heightened standard of proof, sustaining the defense only if Merck proved it by "clear and convincing evidence." *Id.* at 285–86. To prevail at summary judgment, Merck therefore had to prove that "no reasonable juror could conclude that it is anything less than highly probable that the FDA would have rejected Plaintiffs' proposed atypical-fracture warning had Merck proposed it to the FDA in September 2010." *Id.* at 295.

Merck lacked the "smoking gun" that the Court of Appeals believed was necessary to make that showing. *Id.* at 294. In the view of the Third Circuit, a reasonable jury could adopt Plaintiffs' theory of FDA dereliction: that the agency believed the science justified a warning on Fosamax's label, but rejected Merck's proposal because of its "offending stress-fracture references," and then neglected (in contravention of its regulatory policies and statutory duties) even to suggest edits that would protect patients from the risk that the FDA supposedly recognized. *Id.* at 299. If that were so, then it is possible that the agency might have approved a differently phrased warning about atypical femoral fractures—and thus Merck could not establish at the summary judgment phase that federal law preempted Plaintiffs' state-law warning claims. *See id.* at 297, 299.

G. Supported by the FDA, Merck Successfully Overturns the Third Circuit's Opinion Vacating This Court's Decision.

Merck petitioned for a writ of certiorari, and the Supreme Court called for the views of the Solicitor General. In support of Merck's petition, the United States explained—in a brief signed by, among others, lawyers representing the FDA's parent agency—that Judge Pisano was right: The FDA rejected Merck's PAS "because the data at that time was insufficient to justify a change," not because of semantic objections to Merck's "proposed text." U.S. Cert. Br., Exhibit 11 at *19, 21; *see also id.* at *21 ("FDA's decision was … based on the lack of adequate data to support a warning."). "[O]nly in October 2010," the agency explained, "after an external task force had completed its report," did the FDA "c[o]me to believe that the information about atypical femoral fractures should be added to the Warnings and Precautions section." *Id.* at *22. For that reason, the United States agreed that federal law forbade Merck to revise its warning label before the report issued, and that Plaintiffs' state-law claims were accordingly preempted. *See id.*

The Supreme Court then granted Merck's petition, and in due course the United States filed another brief supporting Merck. In that brief, the Government acknowledged that Merck had "provided FDA with the relevant scientific data about Fosamax's risks." U.S. Merits Br., Exhibit 12 at *14. And the Government reiterated that the FDA "rejected a change to Fosamax's Warnings and Precautions because the data at that time was insufficient to justify a change." *Id.* at *30, *33. Had the agency believed that a change was warranted, it would have proposed "suggestions for revisions," just as it did to Merck's "proposed Adverse Reactions text." *Id.* at *32. That course would have honored the FDA's regulatory promise to notify manufacturers of "easily correctable deficiencies," and it also would have discharged the FDA's statutory obligation to "engage in expedited discussions" once it receives new safety information that should be incorporated into a drug's label. *Id.* at *32–33; *see also* 21 C.F.R. § 314.102(b); 21 U.S.C. § 355(*o*)(4).

The Supreme Court vacated and remanded the Third Circuit's decision. *Merck*, 139 S. Ct. at 1672. The Court first held that the preemption inquiry is "a legal one for the judge, not a jury." *Id.* at 1672, 1679. It added that "subsidiary factual disputes," including ones "relevant to a court's legal determination about the meaning and effect of an agency decision," likewise belong to the judge, because they are "subsumed within an already tightly circumscribed legal analysis." *Id.* at 1680. Moreover, when answering these questions, a court should not apply a heightened standard of proof; rather, "the judge must simply ask himself or herself" what the right answer is. *Id.* at 1679 (majority op.); *see also id.* at 1685 (Alito, J., concurring in the judgment) (describing *Levine*'s "use of the phrase 'clear evidence'" as "merely a rhetorical flourish").

In addition to rejecting the Third Circuit's holdings on the questions of (i) who decides the preemption inquiry, and (ii) using what evidentiary standard of proof, the Court glossed the scope of preemption in this context. Citing *Levine*, it explained that state-law failure-to-warn claims are preempted if the manufacturer (1) "fully informed the FDA of the justifications for the warning [purportedly] required by state law," and (2) "the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Id.* at 1678. The Court then remanded the case to the Third Circuit for further consideration and application of these standards.

Upon remand, the Third Circuit chose to return the case to this Court to decide "in the first instance whether the plaintiffs' state law claims are preempted by federal law under the standards described by the Supreme Court." Order of Nov. 25, 2019. The Court of Appeals further instructed this Court "to determine the effect of the FDA's Complete Response Letter and other communications with Merck on the issue of whether such agency actions are sufficient to give rise to preemption." *Id.* This brief addresses those questions.

ARGUMENT

I. MERCK HAS ESTABLISHED ITS DEFENSE UNDER THE SUPREME COURT'S TWO-PART STANDARD FOR PREEMPTION IN THIS CONTEXT.

Where the FDA rejects a proposed label change, failure-to-warn claims are preempted if: (1) "the drug manufacturer fully informed the FDA of the justifications for the warning required by state law," and (2) "the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." *Merck*, 139 S. Ct. at 1672. Applying that two-part standard, Plaintiffs' claims are preempted. Indeed, this Court has already so held, in decisions that are perfectly consistent with the Supreme Court's recent opinion.

A. This Court Has Already Held That Merck Met These Two Conditions.

In his original decisions in 2013 and 2014, Judge Pisano held that Plaintiffs' claims were preempted because (1) Merck had fully informed the FDA about the risks of atypical femoral fractures, yet (2) the agency had indicated to Merck that it would not allow a warning about those risks to be added to the label. While the Third Circuit vacated that ruling based on two novel procedural holdings, the Supreme Court vacated those holdings, returning this case to the *status quo ante*. This Court should thus simply reinstate Judge Pisano's judgment, which is consistent in substance and procedure with the Supreme Court's decision (and with the FDA's own views).

First, after a full trial in *Glynn*, Judge Pisano concluded that Plaintiffs "did not show that [Merck] failed to provide all the information it had on femur fractures to the FDA." 951 F. Supp. 2d at 705. And, after the show-cause proceedings, this Court reiterated that the contention that Merck "withheld information from the FDA" was "based largely on speculation." *OTSC Opinion*, 2014 WL 1266944, at *17. Nothing in either of the appellate decisions casts doubt on that finding. To the contrary, the Supreme Court agreed that this is a necessary element of a preemption defense, and confirmed that the district judge is the factfinder. *See Merck*, 139 S. Ct. at 1678–79.

Second, this Court found that the FDA told Merck that it would not approve a change to the Fosamax label. After carefully examining the evidence surrounding Fosamax's regulatory history, Judge Pisano concluded that, "since the FDA rejected [Merck's] PAS, it would not have approved a CBE seeking to add the same language to the label that it just rejected in the PAS." *Glynn*, 951 F. Supp. 2d at 704; *see also, e.g.*, *OTSC Opinion*, 2014 WL 1266944, at *16 (finding "clear evidence that the FDA *would have* rejected a stronger Precautions warning because the FDA *did* reject a stronger Precautions warning"). Judge Pisano rejected Plaintiffs' contrary theory: that the FDA rejected Merck's proposal solely because it took issue with references to "stress fractures" in the proposal, and thus might have accepted a differently worded proposal. *Glynn*, 951 F. Supp. 2d at 704 (finding that "the FDA did not reject the PAS due to [Merck's] use of the phrase 'stress fracture'"); *OTSC Opinion*, 2014 WL 1266994, at *9 n.5 (continuing to find "clear evidence … that the FDA would have rejected a label change that did not use the 'stress fracture' language").

There is no basis to revisit that finding. Again, the Third Circuit vacated this Court's order only because it believed "the question of whether the FDA would have rejected a proposed label change [wa]s a question of fact that must be answered by a jury," subject to a plaintiff-friendly burden of proof. *Fosamax*, 852 F.3d at 285–86. But the Supreme Court then confirmed that Judge Pisano was correct all along—preemption *is* a question "for the judge," even when it involves "contested brute facts," such as those that might shed light on the "meaning and scope of [an FDA] decision." *Merck*, 139 S. Ct. at 1679–80. And, in resolving these questions, there is no place for heightened burdens of proof. *Id.* at 1679. By rejecting the grounds upon which the Third Circuit vacated Judge Pisano's order, the Supreme Court has left the case where it stood in 2014—with a well-reasoned judicial finding that the FDA did not allow a warning about atypical fractures. And, under the Supreme Court's decision, that finding triggers preemption. *See id.* at 1672.

In short, the procedural "problem for Merck" that the Third Circuit identified (*Fosamax*, 852 F.3d at 290) no longer exists. To evaluate preemption, courts must now do exactly what the Third Circuit believed they could *not* do—assess "in the first instance" as a legal matter whether "the FDA would have rejected a change," resolving any relevant subsidiary factual disputes along the way. *Id.* at 297. Because that is precisely how Judge Pisano originally approached the matter, and nothing in the appellate decisions suggests any need to revisit his analysis or conclusions, this Court should now reinstate his decision granting judgment in Merck's favor.

B. Even Considered Afresh, Merck Informed the FDA About the Possible Risks and the FDA Rejected Its Request To Warn About Those Risks

Even if this Court's earlier decisions were not dispositive, the evidence demonstrates the correctness of Judge Pisano's conclusions. Indeed, the subsequent litigation only *confirmed* those conclusions, as the FDA has now expressly agreed with this Court's characterization of its actions and decisions (and has debunked Plaintiffs' revisionist account).

1. The first element of the preemption defense, under the Supreme Court's framework, is that the manufacturer must have "fully informed the FDA of the justifications for the warning required by state law." *Merck*, 139 S. Ct. at 1672. In this litigation, there has never been any serious dispute that Merck kept the FDA informed about the possible link between bisphosphonate use and atypical femoral fractures. As explained above, Judge Pisano found as much. *See Glynn*, 951 F. Supp. 2d at 703, 705; *OTSC Opinion*, 2014 WL 1266944, at *17. On appeal, the Third Circuit acknowledged that "Merck kept the FDA informed" of the "scores of case studies, reports, and articles … published documenting possible connections between long-term bisphosphonate use and atypical femoral fractures." *Fosamax*, 852 F.3d at 275. Plus, the FDA itself has since agreed that Merck "provided FDA with the relevant scientific data about Fosamax's risks." U.S. Merits Br., Exhibit 12 at *14. There is no contrary evidence whatsoever.

Moreover, Plaintiffs have waived any contrary argument several times over. *First*, Plaintiffs took no real issue with this Court's finding in their initial appeal, and thus abandoned the right to challenge it. *See McKesson Corp. v. Islamic Republic of Iran*, 672 F.3d 1066, 1074 (D.C. Cir. 2012) (holding that a party may not "re-litigate" issues after it already had and missed that opportunity in an earlier appeal). *Second*, Plaintiffs failed, in their opposition to certiorari in the Supreme Court, to dispute the factual predicate for Merck's question presented, which asked whether "a state-law failure-to-warn claim [is] preempted when the FDA rejected the drug manufacturer's proposal to warn about the risk *after being provided with the relevant scientific data*." Pet. for Cert. in *Merck*, No. 17-290, 2017 WL 3701808, at *i (August 22, 2017) (emphasis added). Plaintiffs thereby again waived any challenge to that factual premise. *See* S. Ct. R. 15.2 (requiring brief in opposition to certiorari to "address any perceived misstatement of fact … in the petition that bears on what issues properly would be before the Court if certiorari were granted," on pain of "waive[r]"); *District of Columbia v. Wesby*, 138 S. Ct. 577, 584 n.1 (2018) (respondents "waived their right" to "contest [the petitioner's] factual assertions" since they "did not contest them in their brief in opposition"). *Finally*, Plaintiffs said nothing on this issue in their post-remand letter brief to the Third Circuit. *See* Letter Br. of Plaintiffs-Appellants, Dkt. 3113312949 in No. 14-1900 (3d Cir.) ("Plaintiffs' Supp. Br."). For all of these reasons, Plaintiffs cannot now contend that Merck failed to disclose "the justifications for the warning required by state law." *Merck*, 139 S. Ct. at 1672. The first element of the Court's test is satisfied.

2. The next question is whether "the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Id*. at 1678. The FDA did just that when it rejected Merck's request to add a label warning. And the agency did not change its mind until the task force report in late 2010.

The FDA's rejection of Merck's PAS was a direct determination "that the FDA would not approve changing the drug's label to include that warning." *Id.* Again, Merck's PAS "proposed to add language ... to address atypical femoral fractures." *Fosamax*, 852 F.3d at 276. But the FDA, in its CRL, denied that request, explaining that Merck's "justification for the proposed PRECAUTIONS section language is inadequate." Exhibit 2 at A1500. As the Government later explained in one of its *amicus* briefs in this litigation, the FDA thus "reject[ed] [Merck's] proposal to modify" Fosamax's label to "address atypical femoral fractures." U.S. Merits Br., Exhibit 12 at *30. That fact satisfies the second element of the Supreme Court's framework.

Over the next year and half, the FDA drove home to Merck and other manufacturers that the agency was not prepared to approve an atypical-fracture warning, at least until after the task force issued its report. For example, in a March 2010 Drug Safety Communication—the agency's "primary safety communication tool for important postmarket drug safety issues," FDA, Draft Guidance, *Drug Safety Information – FDA's Communication to the Public* 8 (March 2012)—the FDA noted that, after "review[ing]" "[a]ll available case reports and clinical trial data" submitted after its June 2008 request, it concluded that "these data did not show an increase in th[e] risk" of "atypical subtrochanteric femur fractures" "in women using these medications." Exhibit 5 at 1508; *see also id.* (noting that the FDA's review of a separate December 2008 article also "showed that patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures"). Accordingly, although the FDA was "working closely with outside experts, including members of the recently convened" task force, "to gather additional information," it told doctors to "continue to follow the recommendations in the drug label when prescribing oral bisphosphonates." *Id.* So, even after knowing all of the facts and reviewing the matter with care, the FDA as of March 2010 remained committed to the existing label.

Once the task force issued its report—but *only* after the task force issued its report—the FDA was finally ready to allow a change. The same day that the task force recommended that "[p]hysicians and patients … be made aware of the possibility of atypical femoral fractures" in light of "recent observations [that] suggest[ed] that the risk rises with increasing duration of exposure," *First Report*, 25 J. Bone & Mineral Research at 2267, the FDA acknowledged the report and its labeling implications. In contrast with the March 2010 Drug Safety Communication—which had told doctors to continue following the recommendations in Fosamax's label—the FDA's new statement explained that it was now "considering label revisions." Exhibit 9 at A1512.

And, after it completed its review a month later, the FDA ordered such changes. According to its new Drug Safety Communication, this action was "part of" the "ongoing safety review" announced in March 2010, and was based on the FDA's "review[]" of "all available data, including data summarized" in the task force report. Exhibit 10 at A1118–19. In an FDA Media Call that same day, the Deputy Director of the Office of New Drugs made abundantly clear that it was the task force report that had "ma[de] [the agency] confident that this is something that is potentially more closely related to these drugs … than [it] previously had evidence for." Exhibit 6 at A1396.

In light of this overwhelming evidence, it is little surprise that this Court has already found that the FDA's rejection of the PAS conveyed a refusal to permit label revisions until the task force spoke. *See supra* I.A. It is also little surprise that *the FDA itself* has confirmed this account: that the FDA told Merck (and other manufacturers) that it would not approve *any* atypical-fracture warning until after the publication of the task force report. The FDA shares Merck's understanding of the agency's CRL: Through that letter, the "FDA determined that the existing data for atypical femoral fractures" was not "sufficient" to justify a warning. U.S. Merits Br., Exhibit 12 at *30–31. The FDA also shares Merck's understanding of its subsequent statements: The March 2010

Drug Safety Communication made clear that the FDA "had yet to identify an 'increase in [a] risk [of atypical subtrochanteric femur fractures] in women using [bisphosphonates],'" and its October 2010 actions made clear that it "was only [then]—after an external task force had completed its report on the issue"—that, "in FDA's judgment, an update to Fosamax's Warnings and Precautions section to discuss atypical femoral fractures would … have been called for." *Id.* at *33–34. It is hard to imagine clearer evidence that "it would have been impossible under federal law for [Merck] to provide such a warning at an earlier time." *Id.* at *34; *see also Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000) (deferring to agency's views in preemption case).

* * *

Long before the Third Circuit and Supreme Court debated the role of the jury in preemption and the burden-of-proof implications of *Levine*'s "clear evidence" standard, Judge Pisano wrote two opinions that carefully analyzed the evidence and determined that a fully informed FDA had refused to allow Merck to warn about atypical femoral fractures. As it turns out, that was precisely the correct framework for evaluating preemption, and Judge Pisano was the right person to apply the framework. Moreover, his conclusions are unimpeachable on both prongs of the test; indeed, the FDA has since vouched for Judge Pisano's construction of its regulatory scheme and decisions. To apply the Supreme Court's framework "in the first instance," as the Third Circuit directed, thus requires nothing more than reinstituting Judge Pisano's original judgment in Merck's favor.

II. PLAINTIFFS' COUNTERARGUMENTS ARE LEGALLY AND FACTUALLY MISGUIDED.

Throughout this litigation, Plaintiffs have pressed the theory that the FDA's rejection of Merck's proposed warning reflected only the agency's objections to its use of "stress fracture" terminology, and thus should not be understood as a flat rejection of *any* warning about atypical femoral fractures. This Court long ago rejected that construction of the agency's actions, and the evidence against it has only grown after the FDA's entry into this litigation as an *amicus*.

More recently, Plaintiffs have latched onto an innocuous paragraph in the Supreme Court's decision, suggesting that it somehow upended the law in dramatic fashion by limiting preemption analysis to agency decisions that are independently "legally binding." This is both legally wrong and factually irrelevant given the FDA's formal rejection of Merck's proposal in this case.

A. Plaintiffs Misread and Misunderstand the CRL.

From the start, Plaintiffs have argued that the FDA rejected Merck's proposed warning only because that warning referred repeatedly to "stress fractures," which is terminology that the agency admittedly did not favor. That construction of the CRL contemplates the possibility that, had Merck sought to add a warning *without* reference to "stress fractures," the FDA might have allowed it. Plaintiffs therefore take the position that the FDA did *not* inform Merck that it "would not approve changing the drug's label" to warn of atypical femoral fractures (*Merck*, 139 S. Ct. at 1678)—only that Merck's particular proposal, as worded, was unacceptable.

This is a dispute over how to construe the FDA's actions. Merck understands the FDA to have conveyed that it would not approve *any* warning about atypical femoral fractures before the task force report. Plaintiffs understand the FDA to have conveyed a far more limited message. As the Supreme Court clarified, it is for this Court to resolve that dispute concerning "the meaning and scope" of the FDA's decisions and actions, even if doing so requires the resolution of factual disputes. *Id.* at 1680. For at least five reasons, the Court should reject Plaintiffs' construction, and with it their objections to Merck's preemption defense.

First, this Court *already* rejected Plaintiffs' construction, and specifically found that the FDA "did not reject the PAS due to Defendant's use of the phrase 'stress fracture.'" *Glynn*, 951 F. Supp. 2d at 704. That finding was based on a full trial record, including expert testimony by both sides about scientific use of the relevant terminology in 2008. *See id.* at 703–04. There is no reason to revisit that finding now simply because Plaintiffs continue to disagree with it.

Second, if anything the evidence supporting Judge Pisano's conclusion has only *expanded* since 2014. At that point, the Court construed the FDA's actions based on the regulatory context and in light of expert testimony and documentary evidence. Once this case reached the Supreme Court, however, the FDA itself began to participate (through the Solicitor General) as an *amicus curiae*. The United States explicitly represented that the FDA's rejection of Merck's PAS was "based on the lack of adequate data to support a warning," not "because of the warning's use of the term 'stress fractures.'" U.S. Merits Br., Exhibit 12 at *31–32. Nobody could be better situated to explain the "meaning and scope" of the FDA's decisions than the FDA itself. *Cf. Geier*, 529 U.S. at 883.

Third, even setting aside Judge Pisano's decision and the FDA's representations, Plaintiffs' account cannot be reconciled with the statutory and regulatory framework. The FDA's practice is not to reject warnings for "editorial" reasons, but instead to condition approval upon acceptance of certain specified "changes." 21 C.F.R. § 314.105(b); *see also id.* § 314.110(a)(4) (agency will tell applicant how to remedy any remediable deficiencies). *Accord* U.S. Merits Br., Exhibit 12 at *33–34 (explaining these agency practices). That makes sense, because the FDA has its own statutory duty to initiate discussions and order labeling changes if it "becomes aware of new information" that "should be included in the labeling." 21 U.S.C. § 355(*o*)(4)(A), (E). So if a manufacturer proposes warning of a risk that is scientifically justified, but suggests inadequate language, the FDA cannot and will not simply reject the proposal and ignore the problem, leaving patients to suffer in the dark. Rather, it will propose revisions. Conversely, "if the FDA declines to require a label change despite having received and considered information regarding a new risk, the logical conclusion is that the FDA determined that a label change was unjustified." *Merck*, 139 S. Ct. at 1684–85 (Alito, J., concurring in the judgment).

Here, the FDA *did* revise and redline Merck's proposed additions to the Adverse Reactions section of the label (which requires only a looser causal connection to warrant inclusion). *Compare* Exhibit 2 at A1501, *with* Exhibit 1 at A2732. But the agency flatly rejected Merck's proposed addition to the Warnings & Precautions section. And the agency did not exercise its obligation to order a label changes until October 2010, after the task force report convinced it that Fosamax's label should warn about femoral fractures. Exhibit 7 at A1515–19. Had the agency believed a change was justified earlier, it would have taken those steps back in 2009. Viewed in light of this regulatory context, Plaintiffs' construction of the FDA's actions is untenable.

Fourth, Plaintiffs' account cannot be squared, either, with the agency's contemporaneous statements, in and around the time of the CRL. After all, the CRL stated—as one of three distinct "reasons" given for rejection of the proposal—that Merck's "justification" for the warning was "inadequate." Exhibit 2 at A1500. That has nothing to do with semantics; it is a commentary on the absence of a sufficiently clear link between Fosamax and the atypical fractures at issue. *See* U.S. Merits Br., Exhibit 12 at *31 (agreeing with this construction of the CRL). Moreover, the FDA had earlier told Merck that the "conflicting nature of the literature d[id] not provide a clear path forward" on the question of whether to add a warning. *Fosamax*, 852 F.3d at 277. This confirms again that the agency's hesitance was fundamentally scientific, not semantic, in nature.

Finally, the FDA's subsequent statements further refute Plaintiffs' story. In March 2010, the agency stated that its review of the data "did not show an increase in th[e] risk." Exhibit 5 at A1508. And the FDA repeatedly identified the task force report as a game-changer in convincing it that a warning was warranted. *See Fosamax*, 852 F.3d at 278; Exhibit 10 at A1118–19; Exhibit 6 at A1392–93. None of that would make sense if the agency already had sufficient basis, in May 2009, to approve a warning. *Accord* U.S. Merits Br., Exhibit 12 at *32–33 (sharing this inference).

Plaintiffs like to quote a boilerplate recitation, at the bottom of the CRL, of the options that are available by law to the recipient of any CRL: Within one year, Merck could "[w]ithdraw" its PAS, request a "hearing," or "resubmit" and "fully address all the deficiencies listed." Exhibit 2 at A1501; *see also* 21 C.F.R. § 314.110(b). Plaintiffs read that to indicate that the FDA's decision was merely provisional and that Merck could have "fully address[ed]" the deficiencies. But once the CRL is properly understood—for all of the reasons above—as having refused Merck's PAS due to skepticism about the underlying science, that argument is exposed as illusory. There was nothing Merck could do to "fully address all the deficiencies," as the FDA believed the data was not yet sufficient to allow a warning. That is why it did not suggest redlines to Merck's proposal. And that is why the FDA's other communications with Merck, also pursuant to agency regulations (21 C.F.R. § 314.102(a)), *told* Merck to withdraw its request, not to revise it. *See* Exhibit 3 at A1498 (asking Merck to "hold off on the W&P" so the agency could "close out" the PAS).

To be sure, nothing stopped Merck from filing a futile, repetitive application, asking again for the permission that the FDA had just denied. But that does not defeat preemption, given that the agency had already told Merck it "would not approve changing the drug's label." *Merck*, 139 S. Ct. at 1678. The Seventh Circuit's decision in *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803 (7th Cir. 2018), is instructive on this point. There, the FDA rejected a labeling change, and told the manufacturer to "submit a formal meeting request" "[i]f [it] would like to discuss this matter further." *Id.* at 810. The manufacturer did not, but the court ruled that the possibility that it "might have been able to persuade the FDA to change its mind" was too speculative to defeat preemption. *Id.* at 814. The Supreme Court refused to remand *Dolin* for reconsideration in light of its decision in *Merck*, thus signaling that the Court did not view this analysis as inconsistent with its intervening decision. *See Dolin v. GlaxoSmithKline, LLC*, 139 S. Ct. 2636 (2019) (mem.).

In short, the critical premise of Plaintiffs' case—that the FDA had rejected only a warning about stress fractures, not any warning about atypical fractures—cannot withstand scrutiny. This Court already rejected that premise once, and that decision is even more clearly correct now than it was in 2014. There is nothing, factually or legally, to commend Plaintiffs' odious theory that the FDA consciously left patients at risk because it couldn't be bothered to propose a redline.

B. Plaintiffs Misread and Misunderstand the Supreme Court's Decision.

Although the two-step test that the Supreme Court articulated to establish preemption in this context compels the conclusion that Plaintiffs' claims are preempted, Plaintiffs have latched onto an innocuous paragraph in the decision as somehow suggesting narrow limits on the types of agency actions that may be considered for preemption purposes. According to Plaintiffs, only agency actions carrying the force and effect of law can give rise to preemption, whereas informal agency statements must be categorically disregarded. Plaintiffs are legally wrong about what the Supreme Court ruled, and their interpretation is irrelevant anyway on the facts of this case.

The paragraph in question made clear that the question of *how* the FDA may go about communicating its disapproval of a warning was not before the Court. *See Merck*, 139 S. Ct. at 1679 ("The question of disapproval 'method' is not now before us."). The Court therefore offered only the "obvious point" that the FDA's powers are limited to those "within the scope of the authority Congress has lawfully delegated." *Id.* After all, "'an agency literally has no power to act ... unless and until Congress confers power on it.'" *Id.* (quoting *New York v. FERC*, 535 U.S. 1, 18 (2002)). So the "only agency actions that can determine the answer to the pre-emption question" are those actions "taken pursuant to the FDA's congressionally delegated authority." *Id.* The Court then gave a non-exhaustive list of such actions, including "formally rejecting a warning label" through a CRL. *Id.* (citing 21 C.F.R. § 314.110(a)). The point that only *authorized* actions are relevant to preemption is, as the Court said, an "obvious" (and undisputed) one.

Critically, the Supreme Court majority did not accept the more draconian position taken by Justice Thomas in his separate concurrence: that preemption cannot exist in the absence of "final agency action with the force of law." *Id.* at 1683 (Thomas, J., concurring). Indeed, according to Justice Thomas, the rejection of a warning proposal through a CRL could *never* trigger preemption, because a CRL can always be followed by a hearing and thus is not "final agency action." *See id.* Yet the Supreme Court majority specifically identified a CRL as among the FDA's congressionally authorized means to "communicate its disapproval of a warning." *Id.* at 1679 (majority op.). The reality is that Justice Thomas has always held an idiosyncratically narrow view of preemption, which is why he also wrote separately in *Levine*. *See* 555 U.S. at 587 (Thomas, J., concurring in the judgment) (insisting that "agency musings" cannot preempt state law). The Supreme Court did not adopt Justice Thomas's approach in *Levine*, nor did it adopt his approach in *Merck* (which reaffirmed *Levine*). *See Merck*, 139 S. Ct. at 1676–78.[7]

Under the majority's approach, there is no obstacle to Merck's preemption defense. The Court, again, specifically identified "formally rejecting a warning label" as among the authorized FDA actions that would communicate disapproval of a warning. *Id.* at 1679. For that proposition, the Court cited the regulation that provides for the agency to send CRLs. *See id.* (citing 21 C.F.R.

[7] Indeed, Justice Thomas's position would upset well-settled doctrine in various ways. For example, courts have long held that failure-to-warn claims are preempted if the plaintiff has not identified any new, material information that would allow the manufacturer to use the CBE process. *See, e.g.*, *Dolin*, 901 F.3d at 815–16; *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41–43 (1st Cir. 2015). Similarly, courts have also held that the denial of a citizen petition—that is, the denial of a request from a third party that the FDA order a labeling change—can preempt failure-to-warn claims premised on the same risk. *See, e.g.*, *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1101–05 (10th Cir. 2017); *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010). Neither form of preemption would survive on Justice Thomas's approach; there is no final agency action binding the manufacturer with the force of law when the FDA rejects a citizen petition filed by someone else, and there is no final agency action at all when a court concludes that there was no materially new information to allow a change.

§ 314.110(a)). The CRL in this case is the foundation for Merck's preemption defense. Whatever ambiguity may exist about the type of agency actions that trigger preemption, there can be no doubt that a CRL suffices; the Supreme Court directly said so.

Nor is there anything wrong with Merck's secondary reliance on certain other FDA actions and statements. For one thing, all the FDA communications discussed above (including its March 2010 Drug Safety Communication, and its interactions with Merck during the PAS review) fall comfortably within the agency's statutory and regulatory duties. *See, e.g.*, 21 U.S.C. § 355(*o*)(4) (obligation to work with manufacturers to address new safety information); *id.* § 355(r) (obligation to communicate new drug safety information to the public); 21 C.F.R. § 314.102 (obligation to communicate with applicants). There is no credible argument that any of this was *ultra vires* or beyond the scope of the authority that Congress lawfully delegated to the agency; all of it is thus fair game under *Merck*. In any event, the Court need not decide whether these communications *themselves* establish preemption; instead, those actions and statements can be used merely to shed light on the meaning of the CRL—to resolve the dispute between the parties over the meaning and scope of that (indisputably authorized) FDA decision. Nothing in the Supreme Court's decision remotely suggests that these agency actions are off-limits as an *evidentiary* matter.

* * *

The FDA told Merck that it could not warn about atypical femoral fractures. That triggers preemption and defeats Plaintiffs' claims, just as Judge Pisano recognized six years ago. To avoid that conclusion, Plaintiffs first try to mischaracterize the FDA's decision; then they attempt to stop this Court from considering that decision at all or from consulting the contextual pieces of evidence necessary to construe it. All of these efforts are misguided. This case is not complicated. Judge Pisano understood it perfectly last time, and there is no reason for a different result now.

CONCLUSION

For the foregoing reasons, the Court should hold that the failure-to-warn claims of those Plaintiffs injured prior to the task force's September 2010 report, including those failure-to-warn claims disguised as other claims, are preempted.

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Respectfully submitted,

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